At page 8, delete "Scheme 3".

At page 10, line 1, insert --Scheme 3--.

At page 11, structure 8b, delete "(R=Et)" and insert --(R=Pr)--.

At page 22, line 3, delete "8b" and insert --8a--.

Please insert the following as page 27:

--ABSTRACT OF THE INVENTION

The invention provides derivatives of thiazolo[4,5-dl]pyrimidine and their use as inhibitors of proinflammatory cytokines.--

entered on replacement sheet RLR 2-24-00

REMARKS

Reconsideration and withdrawal of the rejection of claims 1, 3-7 and 10-17 is respectfully requested.

Claims 12 and 16-17 having been canceled, and claims 1, 3-7, 11 and 13-14 having been amended, and claims 18-19 having been added, the claims pending in the above-identified application are claims 1-11, 13-15 and 18-19.

Claims 18-19 are supported by claim 11 and by Examples 4 and 8-9.

The amendment to claim 11 is supported by the specification at page 4, lines 1-6.

The specification has been amended to correct minor typographical errors, and to conform the specification to the amended claims. No new matter is added by these amendments.

An Abstract has been supplied, as requested by the Examiner at para. 2 of the Office Action. The Abstract is also enclosed on a separate sheet. The Abstract is supported at page 3, lines 17-23, of the specification.

At pages 3-4 of the Office Action, the Examiner rejected claims 1, 3-7 and 10-17 under 35 U.S.C., first and second paragraphs. These rejections are respectfully traversed.

The amendment to claims 1, 4 and 5-6 to recite that R^3 is optionally substituted with an ester of an amino acid removes the alleged ambiguity in the use of Z twice in claim 1. However, the Examiner is requested to note that the second "Z" is part of the group "OZ" and is defined immediately thereafter as the ester of an amino acid in claims 1, 4 and 5-6. Thus, it is respectfully submitted that the art worker would not be misled as to the definition of either Z in the claims in which it is used.

A

The amino acid ester is now recited to be part of the group R^3. The attachment of the amino acid ester in R^3 is defined at page 5, lines 11-16, and is via the CO_2H group, as in a typical ester. No new matter is added by this amendment. Therefore, withdrawal of this rejection is appropriate and is respectfully requested.

It is respectfully submitted that the amendment to claim 1 to replace NNO(OH) with N(NO)(OH) moots the Examiner's rejection of claim 1 on the basis that NNO(OH) is vague and indefinite as a variable for A. The (hydroxy)(oximyl)amine group is a known isostere for CO_2H. Withdrawal of this rejection is appropriate and is respectfully requested.

The amendment to claim 3 to recite that A is CO_2R^3 is supported by claim 1 and also moots the Examiner's rejection of claims 4 and 6, as set forth in paragraphs 8-9 of the Office Action. The amendment to claim 6 to recite that R^3 is $(C_1$-$C_6)$alkyl substituted with 4-pyridyl is supported by claim 1 and at page 8 of the specification. Therefore, withdrawal of this rejection is appropriate and is respectfully requested.

The amendment to claim 7 to recite that -Z-A is ethoxycarbonylpropyl ($CH_2CH_2CH_2CO_2Et$), moots the Examiner's rejection thereof under 35 U.S.C. § 112(2).

A comma has been placed after SO_2NH_2 in claim 1.

The allowability of claims 2 and 8-9 is acknowledged.

At para. 12 of the Office Action, the Examiner rejected method claims 11-12 under 35 U.S.C. § 112(1) on the basis that "claims 11-14 are the method of treating any and all diseases and/or disorders associated with pathological inflammatory responses for any reason or for autoimmune diseases which is not remotely enabled [emphasis added]." This rejection is respectfully traversed.

As amended, claim 11 is directed to a method for treating a pathological inflammatory response associated with overproduction of proinflammatory cytokines (including TNFα and IL-1) by administering an effective cytokine-inhibitory amount of a compound of claim 1. Thus, claims 11-15 are not directed to treating "any and all diseases and/or disorders associated with pathological inflammatory responses for any reason." Rather, the inflammation must be associated with the release of proinflammatory cytokines, including the inflammatory responses that accompany autoimmune disorders. In other words, the claims are not directed to a cure for

these conditions, but rather are directed to providing a treatment for the inflammatory response by inhibiting TNFα release or the release of other proinflammatory cytokines.

The Examiner is requested to consider that a wide variety of inflammatory pathologies have been linked to overproduction of TNFα or other inflammatory cytokines. The Background of the Invention discusses this mechanism of action of pathological inflammation at length, including some of the conditions in which inflammatory cytokines are pathological. These include ischemia, septic shock, asthma, organ transplant rejection, MS and AIDs. See, specification at pages 1-2.

Representative compounds of the invention have been demonstrated to be potent inhibitors of both TNFα and IL-1, art-recognized proinflammatory cytokines. See page 8 and Examples 4 and 8-9. Compound **8a** was also found to be active in a model for rheumatoid arthritis (Ex. 10). At page 17, the specification contains detailed instructions concerning how to evaluate the compounds for therapeutic utility.

As further evidence that the compounds of claim 1 would be broadly useful against inflammatory conditions, the Examiner is requested to consider the enclosed Rule 132 declaration, executed by the Applicants, noted researchers in Medicinal Chemistry. In the declaration, the inventors report that a representative compound of the invention, 1I-183, inhibited TNFα release in the mouse lung in a model of pulmonary inflammation, following induction with LPS.

The Examiner has further asserted that the claims are overly broad because they "include diseases and/or disorders not even known at this time which may be associated with inflammatory responses." This is certainly the case, if those diseases and/or disorders are ameliorated by inhibition of proinflammatory cytokines. However, the Examiner is requested to note that a valid patent claim can encompass inventions that come into existence after the issuance of the patent claim. Atlas Powder v. DuPont, 224 USPQ 409 (CAFC 1984). This is an infringement question and not an issue related to the examination of a claim for "overbreadth." Thus, it is respectfully submitted that this evidence establishes a reasonable probability that the compounds of claim 1 would function as claimed, which has not been rebutted by the Examiner. Withdrawal of this rejection is therefore appropriate, and is respectfully requested.

It is respectfully submitted that the pending claims have been placed in condition for allowance, and notification to that effect is earnestly solicited.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Assistant Commissioner of Patents, Washington, D.C. 20231 on **December 2, 1999**

Jane Brockschink
Name

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Signature